

## PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY  
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 100871-1 SE	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/SE2003/001602	International filing date (day/month/year) 15.10.2003	Priority date (day/month/year) 18.10.2002
International Patent Classification (IPC) or national classification and IPC C07D 401/12		
Applicant AstraZeneca AB et al		

- This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 3 sheets, including this cover sheet.
- This report is also accompanied by ANNEXES, comprising:
  - ☒ (sent to the applicant and to the International Bureau) a total of 3 sheets, as follows:
    - ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
    - ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
  - ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) \_\_\_\_\_, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

- This report contains indications relating to the following items:

- |                                     |              |   |
|-------------------------------------|--------------|---|
| <input checked="" type="checkbox"/> | Box No. I    | Basis of the report   |
| <input type="checkbox"/>            | Box No. II   | Priority  |
| <input type="checkbox"/>            | Box No. III  | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability  |
| <input type="checkbox"/>            | Box No. IV   | Lack of unity of invention  |
| <input checked="" type="checkbox"/> | Box No. V    | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/>            | Box No. VI   | Certain documents cited   |
| <input type="checkbox"/>            | Box No. VII  | Certain defects in the international application  |
| <input type="checkbox"/>            | Box No. VIII | Certain observations on the international application   |

Date of submission of the demand 30.04.2004	Date of completion of this report 02.02.2005
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. +46 8 667 72 88	Authorized officer Carolina Gómez Lagerlöf/BS Telephone No. +46 8 782 25 00

Form PCT/IPEA/409 (cover sheet) (January 2004)

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# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/SE2003/001602

## Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on a translation from the original language into the following language \_\_\_\_\_, which is the language of a translation furnished for the purposes of:

- ☐ international search (under Rules 12.3 and 23.1(b))  
☐ publication of the international application (under Rule 12.4)  
☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-9 \_\_\_\_\_ as originally filed/furnished

pages\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_

pages\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_

☒ the claims:

pages \_\_\_\_\_ as originally filed/furnished

pages\* \_\_\_\_\_ as amended (together with any statement) under Article 19

pages\* 10-12 received by this Authority on 07.12.2004

pages\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_

☐ the drawings:

pages \_\_\_\_\_ as originally filed/furnished

pages\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_

pages\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages \_\_\_\_\_

☐ the claims, Nos. \_\_\_\_\_

☐ the drawings, sheets/figs \_\_\_\_\_

☐ the sequence listing (*specify*): \_\_\_\_\_

☐ any table(s) related to the sequence listing (*specify*): \_\_\_\_\_

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages \_\_\_\_\_

☐ the claims, Nos. \_\_\_\_\_

☐ the drawings, sheets/figs \_\_\_\_\_

☐ the sequence listing (*specify*): \_\_\_\_\_

☐ any table(s) related to the sequence listing (*specify*): \_\_\_\_\_

\* If item 4 applies, some or all of those sheets may be marked "superseded."

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/SE2003/001602

**Box No. V** Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

## 1. Statement

Novelty (N)	Claims	<u>1-14</u>	YES
	Claims		NO
Inventive step (IS)	Claims	<u>1-14</u>	YES
	Claims		NO
Industrial applicability (IA)	Claims	<u>1-14</u>	YES
	Claims		NO

## 2. Citations and explanations (Rule 70.7)

The claims relate to a process for production of 5-methoxy-2-  
[[ (4-methoxy-3,5-dimethyl-2-pyridyl)-methyl]-thio]-1H-  
benzimidazole.

During the search the following document were found:

A WO 9722603

Document A shows a similar process for production of 5-methoxy-2-  
[[ (4-methoxy-3,5-dimethyl-2-pyridyl)-methyl]-thio]-  
1H-benzimidazole.

The document shows the general state of the art.

Thus, claims 1-14 are considered to fulfil the requirements of  
novelty, inventive step and industrial applicability.

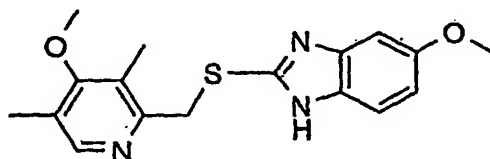
WO 2004/035565

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CLAIMS.

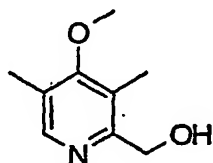
1. A process for the manufacture of 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]-thio]-1H-benzimidazole of formula I



from (4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl alcohol comprising the following reaction steps carried out in a consecutive order in one main solvent system without isolation of the intermediates formed during the process

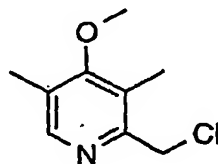
Step 1:

reacting (4-methoxy-3,5-dimethyl-2-pyridinyl)methyl alcohol (pyr methyl alcohol) of the formula Ia



Ia

with a chloro-dehydroxylating agent, providing (4-methoxy-3,5-dimethyl-2-pyridinyl)methyl chloride (pyr methyl chloride) of the formula Ib



x HCl

Ib;

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AMENDED SHEET

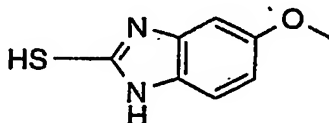
WO 2004/035565

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Step 2:

reacting (4-methoxy-3,5-dimethyl-2-pyridinyl)methyl chloride of the formula Ib, prepared in Step 1 above, with 2-mercapto-5-methoxybenzimidazole (metmercazole) of the formula Ic



Ic

in the presence of a base, providing 5-methoxy-2[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (pyrmetazole) of the formula I

characterized in that the solvent system, common for the whole reaction sequence, comprises water immiscible organic solvent with a specified amount of between 0.3 and 5.5 mg water / ml water immiscible organic solvent added.

2. A process according to claim 1 wherein the water immiscible organic solvent is toluene.

3. A process according to claim 1 wherein the water immiscible organic solvent is ethyl acetate.

4. A process according to claim 1, characterized in that the specified amount of water is present from the start of the reaction according to Step 1.

5. A process according to any one of claims 1 and 4, characterized in that the specified amount of water is added during the charging of the chloro-dehydroxylating agent in the reaction according to Step 1.

6. A process according to any one of claims 1 to 5, characterized in that the specified amount of water is added after charging of the chloro-dehydroxylating agent in the reaction according to Step 1.

5 7. A process according to claim 1, characterized in that the specified amount of water is 0.3 – 5.0 mg/ml of water immiscible organic solvent.

8. A process according to claim 1, characterized in that the specified amount of water is 0.4 – 2.4 mg/ml of water immiscible organic solvent.

10 9. A process according to claim 1, characterized in that the specified amount of water is 1.0 – 2.4 mg/ml of water immiscible organic solvent.

10 10. A process according to any one of claims 1 to 9, characterized in that the reaction according to Step 1 is carried out at a temperature between -5°C and +45°C.

11. A process according to any one of claims 1 to 9, characterized in that the temperature is between -5°C and +35°C.

20 12. A process according to any one of claims 1 to 9, characterized in that the temperature is between +10°C and +35°C.

13. A process according to any one of claims 1 to 9, characterized in that the temperature is between +25°C and +35°C.

25 14. A process according to any one of claims 1 to 13, characterized in that the chloro-dehydroxylating agent is thionyl chloride.